hematopoietic cells, is significantly overexpressed in GBM. It is believed that LYN promotes migration of cancer cells, thus advancing the malignancy. This research addresses computational design of small druglike molecules that could potentially inhibit LYN and thus stave off the cancer advancement. LYN has a very similar binding site to the polo-box domain (PBD) in Polo-like kinase 1 (Plk1). Plk1 is a main regulator of mitosis. Considering the key cellular roles of both LYN and Plk1, it is important to design inhibitors that will specifically bind to LYN. In this work, physical and chemical properties of the binding sites of LYN and Plk1 were investigated and compared. Pertinent atomic distances within the LYN binding site were found to be smaller than those within the PBD of Plk1. The two sites also differed in their flexibilities. By utilizing the differences, novel molecules were designed that could potentially bind LYN with higher affinities than they could Plk1. Previously designed molecules that bonded both LYN and Plk1 were used as initial templates to design more specific inhibitors. Potential toxicities and drug-likeness of the molecules were evaluated. Molecules with no implied toxicities and optimal druglike properties were used for docking studies. Molecules that made the most stable docking configurations with LYN and with no other kinases were identified as LYN-specific. Binding energies of the stable complexes that these molecules formed with LYN were calculated. Possible utilization of the designed molecules against tumors with overexpressed LYN is discussed.

2068-Pos Board B798

Effect of Crystal Meth and Ecstasy Enantiomers on Function of Dopamine Transporters

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The complexities of the brain are hidden in the always active neuron communication. The propagation of the neuron signals is carried out by neurotransmitters. It is obvious why the signals activation is important but the signal quenching is just at important in proper brain function. The length of the stimuli and in turn the intensity are controlled by the neurotransmitter transporters.
The clearing of the neurotransmitters from the synapse is the responsibility of transporters. Each neurotransmitter has its specific transporter. The main ones being Serotonin, Dopamine, and Norepinephrine Transporters (SERT, DAT, and NET). As a class of secondary transporters the sodium:neurotransmitter symporters utilize a sodium ion gradient to co-transport a neurotransmitter molecule against its gradient. The coupling of the ions favourable free energy to the unfavourable recycling of the neurotransmitters is the crucial step in deciphering the mechanism of transport.
The interaction between the substrate and protein are key to proper transport. However these transporters are very common targets not only for the neurotransmitters but many medicinal and psychedelic drugs. Our focus is on exploring similarities between the substrates and what properties make them likely to target transporters. Also we wish to explore the binding differences experimentally observed in different enantiomers of methamphetamines (crystal meth) and 3,4-methylenedioxymethamphetamine (ecstasy). We have used homology modelling to model hDAT and hSERT in three different conformations (open-to-out, open-to-in, and occluded). These six structures will be used to explore the differences between the S and R enantiomers. Like many biological systems preference is given to one conformation over the other, with S enantiomer being the highly preferred one.

2069-Pos Board B799

Predicting Druggable Sites in Protein-Protein Interfaces using *FindBindSite*

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Significance: Aberrant protein-protein interactions are a hallmark of disease and many cancers. Disrupting these interactions is a current therapeutic strategy. However, developing inhibitors for protein-protein interfaces (PPI) remains challenging due to large surface area over which these interactions occur. Computational methods can greatly aid in identifying druggable sites on the PPI enabling rational inhibitor design for PPI.
Approach: We have developed a computational method termed *FindBindSite* (FBS), to identify druggable sites in the PPI starting from free monomer structures. Our method virtually screens a small database of compounds or dipeptides over the entire protein surface and identifies regions with high docked ligand atom density. Densely populated regions are then clustered and scored based on cluster size. The clustering allows us to identify binding surfaces in the interface regions.
Results: FBS was validated 41 protein-protein structures crystallized in complex form. Structures were selected giving preference to free, protein-inhibitor, and then protein-protein complex when structures were not available. We predicted binding sites in interface regions of 71% with a high confidence and 90% with a low confidence using our test set. We tested the performance of FBS on homology models of free monomers achieving a hit rate of 68% when using templates with sequence identity between 20-97%. Applying a 60% sequence identity cutoff we achieved a hit rate of 86%. Using a library of dipeptides we were able to achieve 85% hit rate. We demonstrate that FBS is a useful computational method to predict binding sites in protein-protein interfaces because it uses the probe molecule diversity to span beyond well formed pockets and identify regions where one could likely disrupt any PPIs are likely to occur.

2070-Pos Board B800

Understanding the Interactions of Three Integrins with a Library of Peptides

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Integrin receptors play a critical role in mediating early events in cells adhering to ECM and synthetic peptides on surfaces. To better understand the sensitivity of peptide sequences to a specific integrin types and between integrins we performed a computational analysis. Specifically we began by sequence based homologies between the three integrin receptors (3VI4, 3ZE2, and 1L5G) for which crystal structures are available. Using the homology study as a starting point we developed some hypothesis on potential similarities and differences to be expected with respect to their function. As the next step we performed computational docking simulations of the library of peptides (19) against each of these peptides using Autodock. For these simulations we primarily used the co-crystal structure (integrin/RGD PDB name 3ZE2) implicated binding pocket as the focus of our studies. Based on these docking simulations we have generated a number of different binding ensembles for each peptide for a given integrin receptor. From the top docking configurations (based on visual inspection, grouping, and Autodock Binding scores), we then performed steered molecular dynamics simulations to generate a potential of mean force for the peptides against the receptors. These values then serve as starting point into a multi-scale simulation study being used to estimate the adhesion of the entire cell to an ECM/functionalized surface.

2071-Pos Board B801

Re-Docking Scheme to Explore Docking Search Space by using Interaction Profiles

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In protein-protein interaction predictions, there are various approaches to obtain near-native 3D structure of protein complexes. One of the most available methods is rigid-body docking process, generating many protein complexes (decoys) as candidates of the native complex.
However, we sometime faced with one of the critical problems to solve, which is a situation of no near-native decoys including a decoy dataset. Even if the bound-state case, in 9 out of 44 protein pairs, we could not obtain near-native decoys. To overcome this situation, we applied interaction fingerprint (IFP) to this problem. IFP method in docking process is originally developed for cluster analysis by comparing among decoys in our previous work [Uchikoga & Hirokawa, (2010) BMC Bioinfor. 11:264]. This method can applied to proteins with large conformation changes, for example, calmodulin. IFP composed of frequencies of interaction between amino acid residues. Therefore, much more different structures can compare each other.
The critical situation of no near-native decoys results from a fact that docking search space is not large enough to obtain near-native decoys. Therefore, we proposed re-docking scheme for exploring docking search spaces by restricting protein surfaces after assembling interaction surfaces of decoys using IFPs. We applied re-docking scheme to several docking cases and will discuss the results.

2072-Pos Board B802

Model of the Nogo: Nogo Receptor Complex

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Several myelin-associated proteins, the neurite outgrowth inhibitor (Nogo), myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin

glycoprotein (OMgp), contribute to inhibit central nerve system (CNS) regeneration after injuries; mainly by blocking axonal regrowth. The neurite outgrowth inhibitor (Nogo-A) is a multi-domain transmembrane (TM) protein. The loop domain, connecting the two hydrophobic C-terminus TM helices, is referred to as Nogo-66. The inhibitory effect of Nogo is established when Nogo-66 binds to its receptor (NgR) on the axon. Based on mutagenesis studies performed in our lab, residues Ser 38, Asn 39, Ser 40, Leu 42, Arg 53 and Arg 54 affected the binding of Nogo-66 to NgR. Arg 53 and Arg 54 are among the most affected residues. On the other hand, combinatorial studies on NgR, Asp 111, Asp 114, Asp 163 are the most residues contributing to the interaction of NgR with Nogo-66 (1). To confirm this observation, High Ambiguity Driven Docking (HADDOCK) expert interface server was used (2). As starting structures for docking studies, we used the crystal structure of NgR (PDB id 1OZN) and the NMR solution structure of Nogo-66 (PDB id 2KO2). The complex structures resulted from HADDOCK studies were in agreement with our mutagenesis studies and provide insight into the mechanism of inhibition.

References:
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2073-Pos Board B803

Biomolecular Recognition Based on 3D Molecular Theory of Solvation

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Protein-protein and protein-ligand recognition plays an essential role in many biomolecular processes. Understanding the mechanisms of protein-ligand binding is also crucial for designing new and optimizing existing therapeutic agents, and in different biotechnological applications. It is well known that solvation effects, including hydrophobicity and solvent mediated hydrogen bonding, are major factors implicated in biomolecular processes. Such processes often involve slow conformational changes and exchange of solvent and ligand molecules between bulk solution and biomolecular cavities.

We develop new approaches for accurate account of molecular solvation effects in protein-ligand recognition and binding, which further extend the ligand mapping protocols based on the molecular theory of solvation, a.k.a. the three-dimensional reference interaction site model with the Kovalenko-Hirata closure (3D-RISM-KH). Based on statistical mechanics, this theory provides a natural link between different levels of coarse-graining details in a multiscale description of solvation structure and thermodynamics, from highly localized structural solvent and bound ligand molecules to effective desolvation potentials and self-assembling nanoarchitectures in solvents of different composition in a range of thermodynamic conditions.

Implemented in the new 3D-RISM-Dock protocol, the theory provides a quantitative estimate of binding affinities, based on a detailed physical description of hydrogen bonding, hydrophobicity, and solvation entropic effects, with full account for molecular specificities, thermodynamic conditions, and concentration effects. The theory accurately predicts the solvation structure of biomolecules. This allows us to incorporate the 3D-RISM-KH description of structural solvation in a new docking protocol. The latter has been successfully applied to predict the binding modes of the periplasmic binding proteins in situations when structural solvation and desolvation effects are of importance. We also show that the 3D-RISM-KH theory provides valuable information on the role of the solvation entropic effects in the ligand binding and large scale conformation dynamics of proteins.

2074-Pos Board B804

Fluctuation Flooding Method (FFM) for Enhancing Conformational Sampling of Proteins

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A simple and powerful method for enhancing conformational transitions of proteins, referred as "Fluctuation Flooding Method (FFM)", is proposed. In FFM, biologically relevant anisotropic fluctuations of proteins are firstly characterized by the principal component analysis (PCA) from trajectories of molecular dynamics (MD) simulations. Then largely fluctuated snapshots along the anisotropic directions are assumed as candidates that tend to induce conformational transitions with high probabilities and selected as initial structures for Multiple Independent Molecular Dynamics (MIMD) simulations. In MIMD, a series of short time MD simulations are performed with re-generating initial velocities for selected candidates to enhance conformational transitions. Due to the re-organizations of the initial velocities, some of the candidates might make a conformational transition to another meta-stable states. The multiple trajectories from MIMD are characterized by the PCA to extract largely fluctuated snapshots as candidates for the next MIMD step. These procedures are repeated until distributions of the conformational sampling are well converged. In addition to FFM, Multiple Independent Umbrella Sampling (MIUS) using reference structures selected from MIMD can provide Free Energy Landscape (FEL). FEL calculations by the combination with MIUS enable us to quantitatively determine conformational transition pathways and estimate structural stabilities of newly found meta-stable states.

To assess the reliability of the proposed method, we applied FFM to a toy model and confirmed that probability densities calculated from FFM showed a good agreement with the analytical solution. As an application to a real protein system, we applied FFM to T4-Lysozome in explicit water. Although 1-μs canonical MD failed to sample the closed state, FFM with 10-ns MIMD succeeded in finding conformational transitions from the open to closed states, where the minimum root-mean square deviation between the predicted closed and experimental X-ray structures was 0.76 Å.

2075-Pos Board B805

Accelerating the Molecular Dynamics Sampling of Mutants: A Hierarchical Bayesian Markov State Model Strategy

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Mutational analysis is the bread and butter of experimental protein biophysics; however, in simulation studies, mutational analysis remains a major challenge because the computational costs scale proportional to the number of mutants. We suggest a way out of this connundum, by using large-scale simulation of a wild-type protein as an informative prior on the simulations of mutants. With an ansatz that mutation perturbs the rates of inter-conversion between an unknown subset of the conformational states of the protein, we introduce a Bayesian adaptive simulation framework in which these perturbations are automatically perused and discovered in a maximum expected information gain criterion. Preliminary data suggests that this approach can lead to speedups on the order of ten times in simulations of mutants, by focusing molecular dynamics sampling in regions of phase-space that are perturbed with respect to the wild-type.

2076-Pos Board B806

Predicting HLA-Specific Drug Hypersensitivity with Molecular Docking and Molecular Dynamics Simulations

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Adverse drug reactions are a leading cause of morbidity and mortality with estimated annual in-patient costs of over $100 billion in the US alone. A growing number of the most sever adverse reactions, termed idiosyncratic hypersensitivities, are observed to be immune system mediated with genetic associations to specific patient human leukocyte antigen (HLA) alleles. However, the underlying mechanisms of such genetic associations are still unclear. Improved knowledge of these mechanisms is highly desirable for prognosis and prevention as well as the optimal utilization of drug therapies. Recently, we combined *in silico* and *in vitro* approach to demonstrate that the antiviral drug abacavir can bind inside the antigen binding cleft of HLA B*57:01 and alter its specificity for self-peptides presented to T cells. This finding, which has been independently reproduced, supports a new drug induced "altered peptide repertoire model" for HLA-drug associated hypersensitivities and explains the specificity of abacavir for HLA B*57:01 over other alleles. Here we describe the combined application of structural modeling, molecular docking and molecular dynamics simulations to further examine the generality of this model to additional drugs with known HLA-drug associated hypersensitivities. The predictive power of our *in silico* approach was evaluated with a benchmark containing mixed drug hypersensitivity associated and unassociated HLA alleles. The critical energetic features of HLA-drug binding were further investigated via molecular dynamics simulations. For abacavir, the antiepileptic drug carbamazepine, and the antihyperuricemic drug allopurinol these simulations identified the variant specific residue-wise determinants of HLA-drug interactions. Our studies represent a first step toward the development of preclinical screening processes that aims to highlight drugs with a high risk of causing drug hypersensitivity.